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Review

Understanding the role of primary tumour localisation in colorectal cancer treatment and outcomes

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Abstract Metastatic colorectal carcinoma (mCRC) is a heterogeneous disease with differing outcomes and clinical responses and poor prognosis. CRCs can be characterised by their primary tumour location within the colon. The left-sided colon, derived from the hindgut, includes the distal third of the transverse colon, splenic flexure, descending colon, sigmoid colon and rectum. The right-sided colon, derived from the midgut, includes the proximal two-thirds of the transverse colon, ascending colon and caecum. Sometimes, the rectum is described separately, despite originating from the hindgut, and in many clinical series, the left-sided colon includes only tumours within and distal to the splenic flexure. Differences in the microbiome, clinical characteristics and chromosomal and molecular characteristics have been reported between the right and left side of the colon, regardless of how this is defined. There is now strong evidence from clinical studies in patients with mCRC for the prognostic effect of primary tumour location. The impact of primary colonic tumour location on response to treatment is now under investigation in a large number of clinical studies in patients with mCRC.

In this review, we summarise the microbiome, clinical, chromosomal and molecular differences associated with the primary location of CRC. We present an overview of the proven

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prognostic impact of primary tumour location for patients with mCRC and discuss emerging data for the predictive impact of primary tumour location on clinical outcome.

1. Introduction

In Europe, colorectal carcinoma (CRC) is the second most commonly diagnosed cancer and a leading cause of death [1,2]. Metastatic CRC (mCRC) is a heterogeneous disease with differing outcomes and clinical responses. Over the past 20 years, the clinical outcome for these patients has greatly improved because of the expansion in available systemic therapies and ablative techniques, in addition to improved diagnosis and referral for surgery [3]. However, prognosis for mCRC patients remains poor [3]. Clinical studies, to date, have reported a median overall survival (OS) of approximately 24–30 months, achieved with the aid of multiple lines of treatment followed by best supportive care (BSC) [3].

CRCs can be characterised by their primary tumour location within the colon and rectum [4]. Historically, publications have defined CRCs within three compartments of the gut: distal colon, proximal colon and rectum [4–6]. Right-sided colon carcinomas (RCCs) are located within the colon derived from the embryologic midgut, which encompasses the proximal two-thirds of the transverse colon, ascending colon and caecum (Fig. 1). Left-sided colon carcinomas (LCCs) lie within the colon derived from the embryologic hindgut, which includes the distal third of the transverse colon, splenic flexure, descending colon, sigmoid colon and rectum (Fig. 1). It should be noted that the rectum is sometimes described separately although it embryonically belongs to the hindgut. Most clinical series have used a slightly different definition, with any tumour proximal to the splenic flexure considered a right-sided primary and any tumour from the splenic flexure and distally (including the rectum) considered a left-sided primary. With this definition, at least 63% of patients with CRC have LCC [7].

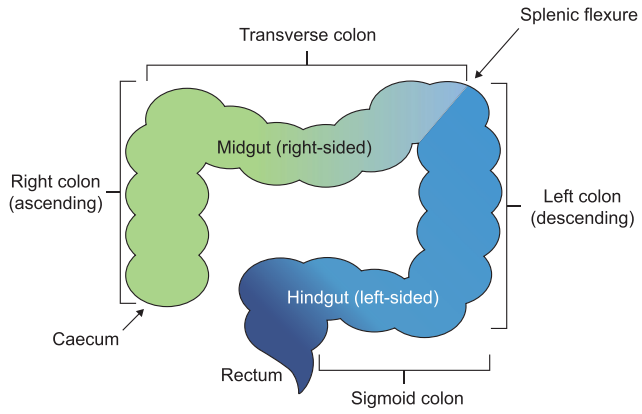

Fig. 1. Schematic diagram of the most commonly used definition of left- and right-sided regions of the colon and rectum.

Prognostic biomarkers predict a likely disease outcome, independent of the treatment received. Strong evidence for the prognostic effect of primary tumour location is available from clinical studies in patients with mCRC [8–13]. Predictive biomarkers may identify patients who are most likely to benefit from a certain treatment. Clinical studies in patients with mCRC are now evaluating the impact of primary colonic tumour location on response to treatment, with a particular focus on biologics [12–17].

Here, we present an overview of the microbiome and molecular differences associated with the primary location of CRC, and we discuss the prognostic and predictive impact of primary tumour location on clinical outcome for these patients.

2. Embryology of the midgut and hindgut

During gastrulation, the right (midgut) and left (hindgut) side of the gut develop from the endoderm and extend along the length of the embryo from the buccopharyngeal membrane to the cloacal membrane [18]. The midgut gives rise to the duodenum distal to the ampulla, the entire small bowel, the caecum, appendix, ascending colon and the proximal two-thirds of the transverse colon [19].

The distal third of the transverse colon, splenic flexure, descending colon and sigmoid rectum and the upper part of the anal canal originate from the hindgut [19]. The most distal portion of the hindgut enters into the posterior region of the cloaca, called the primitive anorectal canal, from which the anal region is derived.

Because both the right and left side of the colon derive from the endoderm [18], embryology does not appear to be the major source of the differences observed in the prognosis of CRC. Distinct gene expression differences, reflecting the midgut and hindgut differences, have been reported between the right and left side of the normal colon, as described later in this article [11,20–22].

3. Microbiome differences between the normal gut and CRC

Limited data are available on the differences of the microbiome within healthy colon tissue, and there are currently no large analyses published on the distinct differences between the transverse and descending colon.